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INTRODUCTION

Bipolar cells in the vertebrate retina: from form to function

The bipolar cell occupies a pivotal position in the retina as the major neuron that bridges the gap between the two synaptic layers of the retina. In the outer synaptic, or plexiform layer, bipolar cells collect their input from photoreceptors, while in the inner synaptic layer, they are presynaptic to both amacrine and ganglion cells, as well as postsynaptic to some types of amacrine cells. There are two main classes of bipolar cells: ON and OFF bipolar cells. The two types can be distinguished both by their function and their morphology. Functionally, OFF cells express AMPA and/or kainate glutamate receptors on their dendrites and possibly NMDA receptors in some lower vertebrates, and so they are depolarized in the dark, although only slightly because the persistent release of glutamate from photoreceptors can desensitize both AMPA and kainate receptors. ON bipolar cells use a metabotropic receptor, mGluR6 that closes a newly-discovered postsynaptic channel, Trpm1, through a G protein coupled mechanism. Consequently, ON bipolar cells are depolarized when light suppresses photoreceptor transmitter release, but this depolarization is short lived, as Trpm1 desensitizes as well. Thus, both ON and OFF bipolar cells have built in mechanisms which insure that signaling is transient. Morphologically, OFF bipolar cell dendrites make synaptic contact with photoreceptors at the base of the presynaptic terminal, while the dendrites of ON bipolar cells make up the central element of the classically described postsynaptic triad complex, flanked on either side by the dendritic processes of two horizontal cells. In the inner retina, the axon terminals of ON and OFF bipolar cells terminate in different sublaminae of the inner plexiform layer. In the mammalian retina, ON bipolar cells can further be divided into those that receive rod input, of which there is one type, sub-serving night vision, and those that are driven by cones, of which there are many, that process photopic and chromatic signals. ON-type rod bipolar cells respond to light with a sustained depolarization indicating that bipolar cells can have both tonic and/or transient light responses.

Recent advances in imaging techniques and in genetic and immunocytochemical labeling of specific cell types have greatly enhanced our abilities to resolve subtypes of both ON and OFF bipolar cells. A challenge for the modern retinal scientist is to assign specific functions to each of these types. In accordance with this goal, the purpose of this special issue is to highlight emerging research and themes regarding both the form and function of bipolar cells. We have chosen to divide the articles by theme rather than by type, and so original research articles can be found along side reviews. Indeed, several of the reviews are hybrids, comprised of both original findings and timely reviews of the literature. The first section of this issue, which focuses on bipolar cell morphology or "form", highlights recent advances in the identification of bipolar cell types, molecular structure and circuitry, with an emphasis on new insights into the circuitry underlying the detection of color. The second section focuses on bipolar cell "function", represented by 4 reviews and 1 research paper. Processing of information at each end of the bipolar cell is considered here using a variety of modern techniques ranging from measurements of single photon responses to exquisitely sensitive measurements of exocytosis of synaptic vesicles.

As mentioned above, the architecture of photoreceptor presynaptic terminals, particular those of the cone terminal, or pedicle, is arranged in a highly stereotypical pattern that is conserved across species. The idealized arrangement of central, lateral, and basal postsynaptic elements is, however, a tremendous simplification compared with an actual cone pedicle, particularly in the primate retina. Now **Herr et al** provide new details of the cone post-synaptic structure. The authors describe post-synaptic densities in addition to the basal contacts between OFF bipolar cell and cone, which they further divide into inner and outer post-synaptic densities. An intriguing hypothesis is that separate types of glutamate receptors are expressed at inner and outer densities, each mediating different aspects of synaptic transmission. The work of **Herr et al** adds an additional layer of complexity to a synapse that is already considered to be the most complex in the central nervous system. Beyond the cone pedicle, we next examine the considerable number of bipolar cell types required to provide a complete picture of the visual world. In the primate retina, 10 types of bipolar cells have been described with each presumably analyzing a specific aspect of the visual world. One reason for the requirement of multiple types of cone-driven bipolar cells is that bipolar cells are color coordinated. At least one type is known to collect input from only short- (S) wavelength cones, and there may be others with a similar specificity. In this issue, **Dacey and colleagues** provide anatomical evidence for the existence of an additional type of cone-driven bipolar cell that they call the giant bipolar cell. Based upon measurements of stratification, dendritic and axonal field area, the authors suggest that the giant bipolar cell may contact large numbers of a single population of cone, perhaps either the long- (L) or medium- (M) wavelength cones, but the specific role of this newly discovered bipolar cell in color vision will await further studies. One difficultly with the use of anatomical approaches to correlate bipolar cell and cone types is that there are currently no antibodies that distinguish between L-wavelength and M-wavelength cones. In this issue, **Schein and colleagues** provide evidence that OFF midget bipolar cells have connections with non-S cones that fall into two groups, distinguished by the total number of contacts, thus representing a way to discriminate L- from M-cones. Evolutionarily, the acquisition of trichromacy is a relatively recent event that is restricted to primarily old world primates, including humans. The S-wavelength cone is quite ancient, as is a second cone, with spectral

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characteristics that are similar to the modern day M-cone. Gene duplication in the second cone, resulted in modern day L- and M-cones. This may also account for the difficulty of generating antibodies that recognize unique epitopes that do not cross-react with both L- and M-cones. Continuing with the theme of color discrimination, **Puller and Haverkamp** review the bipolar cell pathways involved in the generation of color opponency in non-primate dichromats. They suggest that a circuit which includes the blue cone bipolar cells created for short/long wavelength discrimination in dichromats has been retained in the evolution of trichromatic animals. Moving to the inner retina, **Grunert et al** address the circuitry of melanopsin-expressing ganglion cells. Since the discovery that this sparsely distributed but critical type of ganglion cell is intrinsically photosensitive, melanopsin-expressing ganglion cells have been the subject of intense investigation. More recently, melanopsin-expressing ganglion cells have additionally been shown to receive input from extrinsic photoreceptors, but the identity of the bipolar cells that mediates this input was not clear. **Grunert et a**l demonstrate that one type of ON bipolar cell, DB6, provides strong input to ON type melanopsin-expressing ganglion cells, while rod-driven bipolar cells do not.

In addition to understanding their "form", tremendous progress had been made toward understanding bipolar cell "function" as well. Some types of bipolar cells, called midget cells, sample from only one or perhaps just a few cones. But rod-driven bipolar cells sample from 20 or more rods to maximize the detection of dim stimuli. The problem with such an approach is that the noise that is inherent in rods would, if it was passed on to rod bipolar cells, completely swamp the signal. **Trexler et al** examine the impact of nonlinear filtering at the rod to rod bipolar cell synapse on the rod bipolar cell signal-to-noise ratio. They conclude that the position of the filter leads to the removal of noise, making for an improved signal-to-noise ratio compared to the signal-to-noise ratio in rods. However, there is also an inevitable high rejection rate of small single photon responses. The number of responses that are rejected by the synapse is higher than has been reported in other species, perhaps as dictated by the higher convergence of rods onto RBCs in rabbit. Such a model of synaptic filtering has been referred to as throwing out the small babies with the bathwater. Much of what we know about bipolar cell function is drawn from studies carried out in dim light, where the postsynaptic effects of single photon responses can be quantified. However, for diurnal animals such as humans, the natural world is more commonly viewed under photopic conditions, which stimulate the cone pathway. Here, **Burkhardt** reviews studies of the mechanisms by which bipolar cells process cone signals. He argues that bipolar cells cannot be thought of as just discrete ON or OFF types, but when characterized by their functional properties such as contrast gain and spatial resolution, they form an almost continuous distribution. His work provides important insights into the relationship between bipolar cell function and the natural world. It also suggests that bipolar cells are much more versatile and diverse in their functional capabilities than was previously thought.

The synaptic terminal of bipolar cells receives inhibitory input from amacrine cells in the form of reciprocal and lateral GABAergic and glycinergic synapses. **Eggers and Lukasiewicz** review the extensive literature on the properties of these inhibitory synapses that modulate the light responses of ganglion cells and the output of bipolar cells. A prominent portion of this inhibitory input is mediated by $GABA_C$ receptors, which unlike $GABA_A$ receptors, have a high affinity for GABA, slow activation kinetics, and do not desensitize. They are thus well suited to mediate tonic inhibitory currents that will influence the excitability of bipolar cells and thus the release of glutamate at their synaptic terminals. In addition, bipolar cell presynaptic glutamate transporters that are coupled to a chloride conductance may also contribute to a negative feedback control of bipolar cell output to ganglion and amacrine cells. Eggers and Lukasiewicz show that rod bipolar cell inhibition is mediated mostly via $GABA_C$ receptors, whereas OFF cone bipolar cell inhibition is mostly via glycinergic inhibition. Distinct classes of bipolar cells thus use different receptor types and mechanisms for inhibition.

This special issue ends with two reviews on the extensive work being done using zebrafish, mouse, rat, and goldfish bipolar cells. The rapid development of the transparent zebrafish embryo has made it a favorite vertebrate model to study retinal development. The availability of mutant strains and transgnic lines, as well as the use of morpholinos to knock down specific molecules, makes it a powerful model system to also study the function of retinal genes and how they influence visually guided behaviors. **Connaughton** reviews the morphological and physiological studies done on different types of zebrafish bipolar cells. Bipolar cell voltage- and ligand-gated currents are reviewed and reveal that bipolar cells are endowed with a rich repertoire of ion channels in their plasma membrane that sub-serve a variety of functions. Neuromodulators, like dopamine and endocannabinoids, are also discussed as important mediators of retinal adaptation to different ambient light levels. Finally, **Wan and Heidelberger** review recent studies on synaptic vesicle release from mammalian bipolar cell terminals. They show that mouse bipolar cells can be studied using paired recordings in retinal slices and also with time-resolved membrane capacitance measurements. Several interesting comparisons with goldfish Mb bipolar cells (mixed cone and rod input cells that have an unusually large presynaptic terminal) are made with regard to their Ca^{2+} currents, vesicle pool size, vesicle pool depletion rates, short-term plasticity, and recovery from synaptic depression. The kinetics of exocytosis and endocytosis of synaptic vesicles can be monitored in real time from single isolated cells using membrane capacitance measurements. The Ca^{2+} dependence of release and of the recruitment of the readily releasable pool of synaptic vesicles is discussed, as well as novel data on the kinetics of dynamine-dependent endocytosis. This issue thus covers fully the physiology and diversity of bipolar cells, from the elaborate branching of the dendritic tree to the intricate roots of the bipolar cell synaptic terminal, a cell type that has indeed borne a lot of beautiful fruit for retinal neuroscience.

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